ORIGINAL ARTICLE 10.1111/j.1469-0691.2004.01057.x

Antibiotic resistance of *Escherichia coli* from community-acquired urinary tract infections in relation to demographic and clinical data

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ABSTRACT

This prospective study determined the antibiotic susceptibility of 164 isolates of *Escherichia coli* from the urine of 164 patients (112 female, 52 male; mean age of 54.12 years) with community-acquired urinary tract infection (UTI). Half of the isolates were from uncomplicated UTI and half from complicated UTI (52 males and 34 females). Overall, 57.3% of isolates were resistant to ampicillin, 25% to co-trimoxazole, 20.1% to nalidixic acid, 14% to norfloxacin and ciprofloxacin, and 0% to fosfomycin and nitrofurantoin. Of the 82 isolates from complicated UTI, 16 (19.5%) were resistant to norfloxacin and ciprofloxacin, compared with seven (8.5%) from uncomplicated UTI (p 0.043). Isolates from patients aged >50 years were significantly more resistant than those from patients aged <50 years for nalidixic acid (p 0.007) and the fluoroquinolones tested (p 0.015). Resistance to fluoroquinolones was 25% (13/52) in males and 9% (10/112) in females (p 0.006). For patients with and without previous antimicrobial therapy, there was a significant difference only for resistance to nalidixic acid ($p < 0.001$) and the fluoroquinolones (p 0.011). There were adequate susceptibility rates to fosfomycin, nitrofurantoin and the fluoroquinolones for empirical use in the treatment of acute uncomplicated UTI. In order to interpret cumulative susceptibility data from the primary healthcare setting, it is necessary to take into account the type of UTI (uncomplicated vs. complicated), previous antimicrobial therapy, and the sex and age of each patient.

Keywords Antimicrobial resistance, *Escherichia coli*, community-acquired infection, quinolones, resistance, urinary tract infection

Original Submission: 27 May 2004; **Revised Submission:** 28 September 2004; **Accepted:** 17 October 2004

Clin Microbiol Infect 2005; 11: 199–203

INTRODUCTION

Acute uncomplicated cystitis is a significant problem in healthy non-pregnant women [1], with *c*.7 million community-acquired uncomplicated urinary tract infections (UTIs)/year in women in the USA [2]. In a recent prospective study in the USA, the incidence in young women was 0.5–0.7/person/year [3]. Among outpatients, *Escherichia coli* is the primary urinary tract pathogen, accounting for 75–90% of isolates from uncomplicated UTI [4]. In many cases, acute uncomplicated UTI in women is managed effectively and safely by empirical antibiotic therapy without the need for a urine culture. The rationale for this approach is based on the narrow and predictable spectrum of aetiological agents and their susceptibility patterns [5]. Laboratory testing is normally undertaken only when empirical therapy fails.

Knowledge of local susceptibility trends is an important consideration when selecting empirical therapy for UTI. The Infectious Diseases Society of America (IDSA) recommends that physicians obtain information on local resistance rates, and that ongoing surveillance be conducted to monitor changes in the susceptibility of uropathogens [6]. Numerous studies have demonstrated high and/or increasing antibiotic resistance levels in *E. coli* causing community-acquired UTI [7–20], but most in-vitro data come from laboratory-based surveys that often do not define the sex, age, clinical syndrome or other data of interest regarding the patients from whom the urine specimens were collected. In-vitro studies that specifically

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describe the antimicrobial susceptibilities of *E. coli* UTI isolates, and analyse the results in relation to demographic and clinical data, are limited.

In addition, because empirical therapy is being used widely, fewer UTIs are being cultured routinely. Thus, patients for whom culture results are available are likely to reflect a selection bias toward complications, recent treatment, recurrence of infection or suspected resistance. Thus, laboratory samples examined routinely may overestimate the true levels of antibiotic resistance in the community [21–24].

It is necessary to use new strategies to obtain more accurate data. In the emergency service of our hospital, nearly all UTIs treated are community-acquired, and a urine culture is performed routinely on suspicion of UTI. In addition, the Emergency Service sees a greater number of community-acquired complicated UTIs than are seen by a general practitioner, which permits a statistical comparison according to the type of UTI (complicated vs. uncomplicated). The present study assessed the antibiotic resistance of *E. coli* from community-acquired UTI in relation to demographic and clinical data, and the results obtained were compared with those obtained in 2002 for unselected isolates from the urine samples of outpatients.

MATERIALS AND METHODS

This prospective study included 164 isolates of *E. coli* from the urine of 164 patients with community-acquired UTI diagnosed in the Emergency Service of the Hospital de Móstoles (Madrid, Spain) between March 2002 and January 2003.

Susceptibility to ampicillin, gentamicin, fosfomycin, nitrofurantoin, cefazolin, nalidixic acid, norfloxacin, ciprofloxacin, and trimethoprim-sulphamethoxazole (co-trimoxazole) was determined using doubling dilutions in Mueller-Hinton broth in a commercially available microdilution system (Wider; Francisco Soria Melguizo SA, Madrid, Spain) [25]. The panels were inoculated with a standardised inoculum using a rehydrator-inoculator according to the guidelines provided by the manufacturer. The inoculum was prepared with the Prompt inoculation system (Francisco Soria Melguizo SA). After overnight incubation, the panels were introduced into the Wider system, which comprises a reader module and a data analysis module. Growth parameters in susceptibility testing wells were analysed in comparison with those in positive and negative control wells. The MIC of each antibiotic was defined as the lowest concentration with an absence of bacterial growth. For categorisation purposes, MICs were interpreted by NCCLS guidelines [26]. Intermediate and resistant results were grouped together for data analysis. Quality control was assured by including *E. coli* ATCC 25922 in every batch. All MIC determinations for this strain were within the ranges given by NCCLS for the antibiotics included in this study.

The clinical records of the 164 patients were reviewed to obtain demographic data (age and sex) and clinical data that enabled classification of the UTI as complicated or uncomplicated. Uncomplicated UTI refers to infection in a structurally and neurologically normal urinary tract. Complicated UTI refers to infection in a urinary tract with abnormalities. Cystitis describes the syndrome involving dysuria, frequency, urgency, and occasionally, suprapubic tenderness. Acute pyelonephritis describes the clinical syndrome characterised by flank pain or tenderness, or both, and fever, often associated with dysuria, urgency and frequency [27]. Antimicrobial therapy within the preceding 3 months was also recorded.

Differences in antibiotic resistance between different patient groups, together with calculation of the odds ratio (OR) and 95% confidence interval (CI), were analysed by the χ-square test or Fisher's exact test using SPSS software v.9.0 (SPSS Inc., Chicago, IL, USA). A two-tailed p value of ≤ 0.05 was considered significant. Data were obtained from the hospital laboratory concerning the sensitivity of *E. coli* isolates from outpatient urine samples during the year 2002.

RESULTS

The 164 *E. coli* urinary isolates were from 112 women and 52 males (mean age of 54.12 years; SD 21.15 years; range 17–91 years), with 82 (50%) from uncomplicated UTI (82 females; mean age, 46.34 years; SD 22.1 years) and 82 (50%) from complicated UTI (52 males and 34 females; mean age, 61.9 years; SD 17.02 years). Of the 82 patients with complicated UTI, five (6.1%) presented with kidney and urethral calculus, 13 (15.8%) with disorders of the urinary tract (11 anatomical and two functional), eight (9.8%) had urinary catheters, 14 (17.1%) suffered from diabetes mellitus, and 11 (13.4%) were immunosuppressed. Of the 82 women with uncomplicated UTI, 63 had acute cystitis (mean age, 50.14 years; SD 22.88 years) and 19 had acute pyelonephritis (mean age, 33.74 years; SD 13.18 years).

The antimicrobial resistance of the isolates is shown in Table 1. Of the 164 isolates, 23 (14%) were resistant to norfloxacin and ciprofloxacin. Of the 82 isolates from complicated UTI, 16 (19.5%) were resistant to norfloxacin and ciprofloxacin, compared with seven (8.5%) from uncomplicated UTI (OR 2.6; 95% CI 0.93–7.47; p 0.043). Antibiotic resistance to ampicillin, gentamicin, nitrofurantoin, fosfomycin, cefazolin, nalidixic acid and co-trimoxazole was also compared, but no statistically significant differences were observed. Similarly, no statistically significant differences were observed for any antibiotic when resistance in women with complicated UTI ($n = 30$) and uncomplicated UTI ($n = 82$) was compared.

Table 1. Number (%) of *Escherichia coli* isolates resistant to each of the antibiotics tested

Antibiotic	Total (n = 164)	Complicated UTI (n = 82)	Uncomplicated UTI (n = 82)	p	Susceptibility breakpoint (mg/L)
Ampicillin	94 (57.3%)	48 (58.5%)	46 (56.1%)	NS	≤8
Gentamicin	4 (2.4%)	3 (3.7%)	1 (1.2%)	NS	≤4
Fosfomycin	0	0	0	NS	≤64
Cefazolin	8 (4.9%)	6 (7.3%)	2 (2.4%)	NS	≤8
Co-trimoxazole	41 (25.0%)	23 (28.0%)	18 (22.0%)	NS	≤2/38
Nitrofurantoin	0	0	0	NS	≤32
Nalidixic acid	33 (20.1%)	21 (25.6%)	12 (14.6%)	NS	≤16
Norfloxacin	23 (14.0%)	16 (19.5%)	7 (8.5%)	0.043	≤4
Ciprofloxacin	23 (14.0%)	16 (19.5%)	7 (8.5%)	0.043	≤1

NS, not significant.

Significant differences for the quinolones were found when the resistance of isolates from patients aged ≥50 years was compared with isolates from patients aged <50 years, namely 28% (25/90) vs. 11% (8/74) (OR 3.17; 95% CI 1.25–8.3; p 0.007) for nalidixic acid, and 20% (18/90) vs. 6.7% (5/74) (OR 3.45; 95% CI 1.12–11.3; p 0.015) for the fluoroquinolones tested.

No statistically significant difference was found for any antibiotic when resistance in isolates from uncomplicated UTI was compared in patients aged ≥50 years (n = 29) and patients <50 years (n = 53).

Comparison of the resistance rates according to the sex of the patient showed statistically significant differences for cefazolin (11.5% (6/52) in males compared with 1.7% (2/112) in females; p 0.013) and for fluoroquinolones (25% (13/52) in males and 9% (10/112) in females; p 0.006).

There were no significant differences for any antibiotic between women with uncomplicated cystitis (n = 63) and those with uncomplicated pyelonephritis (n = 19).

When patients who had received previous antimicrobial therapy (n = 27) were compared with those without previous antimicrobial therapy (n = 137), there was a statistically significant difference only for resistance to nalidixic acid ($p < 0.001$) and the fluoroquinolones tested (p 0.011).

Laboratory data indicated that 2061 strains of *E. coli* were isolated from outpatient urine samples during 2002, of which 58.4% were resistant to ampicillin, 6.1% to gentamicin, 30.7% to co-trimoxazole, 29.7% to nalidixic acid, 4.1% to cefazolin, 19.0% to norfloxacin, 19.2% to ciprofloxacin, 2.3% to fosfomycin, and 1.4% to nitrofurantoin.

DISCUSSION

Knowledge of local susceptibility patterns is important for the selection of appropriate empirical therapy for UTI. The IDSA guidelines recommend therapy with co-trimoxazole in settings where the prevalence of resistance is <10–20% [6]. Alternative therapy for uncomplicated UTI in settings with >10–20% resistance to co-trimoxazole may include a fluoroquinolone, nitrofurantoin or fosfomycin [6].

In Spain, published data indicate a high frequency of resistance to ampicillin, co-trimoxazole and the quinolones among *E. coli* isolates from outpatient urine samples [7–9,11,17,19], which seems to indicate that these antimicrobial agents should not be used. However, the data from the present study indicate that fluoroquinolone resistance in *E. coli* is associated mostly with isolates from complicated UTI and/or patients who have received previous antibiotic therapy. The results (8.5% resistance to fluoroquinolones in isolates from uncomplicated UTI) have important clinical implications in the context of the empirical use of these antimicrobial agents. Actual resistance rates are significantly less than those indicated by routine pooled laboratory specimens (*c*.19%). Other studies have shown that factors associated with complicated UTI, such as abnormalities of the urinary tract, an age of >65 years, urinary catheterisation, and previous treatment with quinolones, are associated independently with infections caused by ciprofloxacin-resistant isolates of *E. coli* [28]. There are clearly more uncomplicated than complicated UTIs [24] seen in the primary healthcare setting than by an emergency service, so the present results for fluoroquinolone resistance are particularly relevant in that they provide a more accurate picture of the susceptibility patterns of *E. coli* causing uncomplicated UTI. Traditional surveillance data may have a bias toward over-reporting resistance to some antibiotics in patients with acute uncomplicated UTI, as urine samples sent to the microbiology laboratory by general practitioners are not repre-

sentative of UTI in the primary healthcare setting [24]. A recent study [29] found that the frequency of urinalysis requests has declined over time, which probably corresponds with a decline in urine culture and susceptibility testing. This decline will have the unintended effect of decreasing the amount of information available for assessment of local resistance trends [29].

Comparing the results obtained for isolates from uncomplicated UTI with those obtained in 1997–98 in the same area by the same method [30], an increase in resistance to quinolones was observed. Increasing fluoroquinolone resistance among urinary *E. coli* has also been documented in studies in other countries [12,18]. Indeed, in a study in the USA, ciprofloxacin was the only agent studied that demonstrated a consistent stepwise increase in resistance from 1995 (0.7%) to 2001 (2.5%) [18]. An increase in the prescription of fluoroquinolones for uncomplicated UTI in the USA may be contributing to this observation [29]. Based on the data from the present study, the quinolones are currently a valid option for empirical therapy of uncomplicated UTI, but careful use is recommended to avoid the selection and spread of resistant strains.

In conclusion, data from local laboratories exaggerate the fluoroquinolone resistance problems among *E. coli* urine isolates from general practice. In acute uncomplicated UTI, fosfomycin, nitrofurantoin and the fluoroquinolones show adequate rates of susceptibility for empirical use. For optimal interpretation of cumulative susceptibility data in the primary healthcare setting, it is necessary to take into account the type of UTI (uncomplicated vs. complicated), as well as the sex and age of each patient.

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